Case Report

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A case report and review of literature on the role of automated red cell exchange in managing sickle cell crisis in India

Vinu Rajendran, Archisha Kalra, Ashna George, Deepika Chenna, Ganesh Mohan, Shamee Shastry

Abstract:

Red cell exchanges (RCE) help in the treatment of complications of sickle cell anemia (SCA) by reducing the viscosity of blood and improving the oxygen-carrying capacity. We present a case of sickle cell crisis (SCC) managed with automated RCE and also reviewed the literature to assess the utilization and clinical efficiency of this therapy in India. A 19-year-old gentleman diagnosed with SCA presented with acute chest syndrome. Hemoglobin (Hb) was 8.8 g%, hematocrit (HCT) was 24%, and HbS was 90%. As there was worsening of symptoms with conventional management, the patient underwent two procedures of automated RCE. The clinical condition of the patient was improved, HbS was reduced to 16% and HCT was remained at 21% postprocedure. Articles on automated RCE in SCA conducted in India were reviewed and four articles were analyzed based on the search strategy. All the included articles concluded automated RCE as an effective procedure for complications of SCA. Common indication in India was SCA patients undergoing surgery as a prophylactic measure. Automated RCEs are promising as an acute treatment for indicated sickle cell complications. This therapy is underutilized in the Indian scenario, especially in patients with SCC.

Keywords:

Erythrocytapheresis, Hb, HbS, hemolytic anemia, red cell depletion, red cell exchange, sickle cell anemia, sickle cell crisis, sickle cell disease

Introduction

Sickle cell disease (SCD) is an inherited red cell disorder due to a point mutation in the 6th codon of the beta-globin chain of hemoglobin (Hb) wherein a single glutamic acid is substituted by valine.[1,2] Sickle cell anemia (SCA) is a homozygous expression while sickle cell trait is the heterozygous form. This disease is characterized by the presence of HbS, abnormal Hb that polymerizes at low oxygen concentration to form pseudo-crystalline tactoids resulting in the sickling of the red cells and loss of deformability.[3] This condition facilitates hemolysis and small-vessel occlusion. SCA usually manifests with the features of anemia and the complications of abnormal Hb. The patients often require hospitalization in view of the acute complications described as sickle cell crisis (SCC) which includes vaso-occlusive crisis (acute painful crisis), acute chest syndrome, hemolytic crisis, splenic sequestration crisis, aplastic crisis, hepatic crisis, priapism, and dactylitis.[4]

Automated red cell exchanges (RCE) are procedures where abnormal red cells are replaced by normal red cells using the automated apheresis equipment. This procedure not only aids in reducing the overall viscosity of blood but also provides

Department of Immunohematology and Blood Transfusion, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

Address for correspondence:
Dr. Deepika Chenna, Department of Immunohematology and Blood Transfusion, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India.
E-mail: deepu.kkd@gmail.com

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needed oxygen-carrying capacity and thereby helps in the treatment and prevention of complications of SCA. We present a case of SCC managed with RCE in an intensive care unit (ICU) setting in a tertiary care center. We have also reviewed the literature to assess the utilization and clinical efficiency of this therapy in India.

Case Report

A 19-year-old gentleman, who was a known case of SCD for 2 years, presented with low-grade intermittent fever, occipital headache, and multiple joint pain for 4 days relieving on medication. The patient further developed dyspnea and was admitted to our hospital for evaluation. There were two previous episodes of acute pain crisis in a period of 1 year and were managed conservatively. There was no relevant family history. On examination, the patient was drowsy and responding to commands. The temperature was 99.6°C; pallor (+); pulse rate was 56/min; systemic blood pressure was 100/60 mm Hg; tachypnea was present; SpO2 was 97% with room air. No abnormal findings in the cardiovascular system, central nervous system, and gastrointestinal system. No splenomegaly was observed. Basic laboratory investigations revealed Hb as 8.8 g/dl; hematocrit (HCT) as 24%, platelet count as 1,53,000/µL and total leukocyte count as 13500/µL. Peripheral smear showed the presence of sickle cells (2+), anisocytososis (+), polychromasia (2+) poikilocytosis (+), elliptocytes (few), spherocytes, and few target cells. The immunohematological tests revealed the blood group as A Rh D positive and the red cell irregular antibody screen was negative. Arterial blood gas analysis was normal. There were indirect hyperbilirubinemia and markedly elevated Lactate Dehydrogenase (>1000). A splenic infarct was observed in the upper pole of spleen in the ultrasonography of the abdomen. The sickle test was positive and sickle cell percent was 90%. As there was a fall in oxygen saturation (SpO2 92%), the patient was given minimal oxygen supplementation.

In spite of conventional treatment with intravenous hydration, oxygen supplementation, hydroxyurea, opioid analgesia, and comfort measure, his clinical condition worsened. The patient was shifted to ICU for further management and was put on a noninvasive ventilator for the falling oxygen saturation. Chest radiograph showed bilateral infiltrates suggestive of pneumonia. His blood culture was negative. C-reactive protein and procalcitonin were high. The patient was started on the oral antibiotic Azithromycin empirically. There was also a gradual drop in Hb and platelet count [Figure 1]. Tropical fever workup in view of thrombocytopenia revealed dengue IgM positive. Hb electrophoresis demonstrated HbS as 90%. The provisional diagnosis was made as SCA with acute

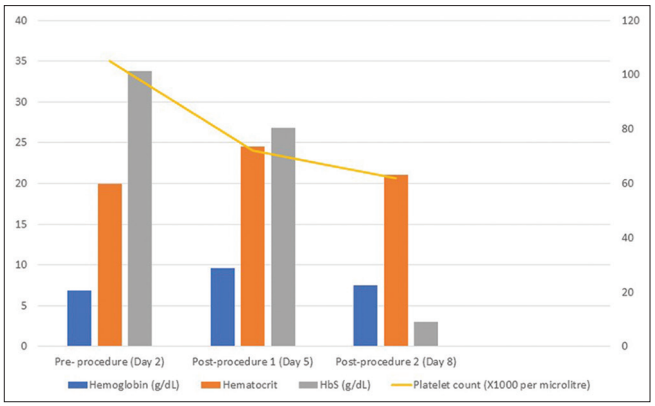

Figure 1: Laboratory parameters through the course of red cell exchange

chest syndrome, pain crisis, and hemolytic crisis, dengue fever, and community-acquired pneumonia. The patient was considered for RCE in view of the worsening of the SCC and nonrespondence to the conventional management including hydroxyurea. In this case, the patient presented with acute chest syndrome not manageable with the conventional management with worsening of symptoms thus fitting him into the category II GRADE 1C recommendation of American Society for Apheresis (ASFA) 2019 guidelines.

Two procedures of automated RCE were performed using the Spectra Optia® Apheresis System machine of Terumo BCT on days 5 and 8 of the admission. The targeted fraction of cells remaining (FCR) was 33% to reduce the HbS to <30% and maintain HCT to 24% as per the institute protocol. Based on the weight of 42 kg, the total blood volume was estimated as 3150 ml. The estimated volume to be exchanged was calculated as 945 mL for the first procedure. A total volume of 962 ml was removed and replaced with around 950 ml (4 units) of packed red cells. The HbS was reduced to 26.8% after the first erythrocytapheresis and second procedure was planned in view of the persisting clinical condition. For the second procedure, 1260 ml was removed and replaced with 3 unit packed red cells (730 ml) and one unit (500 ml) of 0.9% normal saline. HbS was reduced to 16% following second procedure and the FCR was 20.2%. HCT following the procedure was 21.1. All the packed red cells issued were ABO and RhD matching, AntiHuman globulin phase crossmatch compatible, <5 days old, leukoreduced, and tested negative for sickling. The clinical condition of the patient improved following the second procedure and was able to wean off from the noninvasive ventilator after 2 days and was transferred back to the ward. SpO2 was improved to 98% at room air. The clinical condition also improved evidenced by improvement in joint pain and dyspnea. The patient was discharged with oral hydroxyurea and other supportive oral medications on day 17. Currently, the patient is doing well and is on regular follow-up.

Discussion

This was a case of SCA with acute chest syndrome in the acute painful and hemolytic crisis triggered by infection well managed by automated RCE. Hypoxia, dehydration, infections, cold exposure, and stress are some of the identified factors which trigger SCC.[4] Patients with SCC requiring hospitalization are managed with intravenous or oral opioid analgesics, intravenous hydration, oxygen supplementation, and comfort measures.[5-7] Adjuvant therapy such as hydroxyurea, antihistamines, anxiolytics, and antiemetics are also considered for the management. Empirical antibiotics may be considered for any presence of bacterial infection.[5-7] Simple transfusions are suggested when the main symptoms are related to anemia while RCEs are considered mainly to prevent and treat the complications related to HbS.[8-10]

RCEs are suggested as the treatment of choice in patients with sickle cell disease presenting with acute stroke, severe acute chest syndrome with hypoxia, rapid progression of symptoms, severe sickle cell hepatopathy, acute multiorgan failure syndrome, severe priapism, and before moderate to severe risk surgical procedures.[9-15] As per the ASFA guidelines, RCE in sickle cell disease is used in acute and nonacute conditions.[16] However, the category of indication and GRADE of recommendation varies in each condition and is listed in Table 1. Chronic RCEs are considered in recurrent pain crisis and acute chest syndrome, nonrespondence or intolerance to hydroxyurea, and stroke prevention.[9,12]

RCEs can be modified as red cell depletion where the red cells removed are replaced with colloids or crystalloids ensuring isovolumic hemodilution. This procedure can reduce donor exposure and there will be improved efficacy of HBS removal as well.[17,18] However, minimum HCT value varying from 21 to 24% is a prerequisite for the procedure.[19]

Reports from India

A literature review was carried out by two independent reviewers VR and DC based on the Preferred Reporting

Table 1: Category and grade recommendations for red cell exchange in sickle cell disease (Adopted from American Society for Apheresis Guidelines)[16]

SCD	Indication	Category	Grade
Acute	Acute stroke	I	1C
	Acute chest syndrome, severe	II	1C
	Other complications	III	2C
Nonacute	Stroke prophylaxis	I	1A
	Pregnancy	II	2B
	Recurrent vaso-occlusive pain crisis	II	2B
	Preoperative management	III	2A

SCD=Sickle cell disease

Table 2: Various characteristics of the sickle cell anemia cases in India managed by automated red cell exchanges

Author and year	Article type	Number of patients	Indication	Number of procedures	Preprocedure HbS	Postprocedure HbS	Percent reduction of HbS (%)	Preprocedure HCT	Postprocedure HCT	Clinical outcome
Gupta *et al.*,[21] 2020	Case report	1	SCA with acute chest syndrome and septic shock	1	76	9.2	87.9	29	31	Improved
Choudhary *et al.*,[23] 2021	Retrospective study	5	4 patients-SCD with crisis 1 patient-SCD posted for hemiarthroplasty	3 patients-twice 2 patients-once	68.4 (44.4-82.8)	16.3 (9.2-23.8)	76.2	26.4 (20.2-35.4)	29.2 (18.2-38.5)	Improved in all 5 cases
Daniel *et al.*,[22] 2016	Retrospective study	18	SCD posted for hemiarthroplasty	1	73-85	22-29	67.7	NA	NA	Improved in all 18 cases
Aggarwal *et al.*,[20] 2020	Case report	1	SCD posted for hemiarthroplasty	1	65.4	25.6	60.8	34.5	35	Improved

NA=Not available, SCD=Sickle cell disease, SCA=Sickle cell anemia, HCT=Hematocrit, HbS=Hemoglobin S

Items for Systematic Reviews and Meta-Analyses guidelines for a systematic review. The search string strategy was developed by AK and was evaluated for errors and omissions by the research team members. The initial search strategy was developed in Medline and was adapted for Scopus and Google Scholar with restriction in search dates from year 2000 to 2022. Search themes used were "Red cell exchange" and "Sickle Cell Disease" and both the themes were joined using Boolean operator "AND". For the "Red cell exchange" theme, we used "red cell exchange", "erythrocytapheresis" and "red cell apheresis" as the keywords. For the "sickle cell disease," we used "sickle cell disease," "sickle cell anemia," and sickle cell crisis as the keywords. We have included case reports, case series, and original research conducted in India written in the English language and published between January 2000 and May 2022 on automated RCE. Preclinical trials such as *in-vitro* trials, animal studies, unstructured reviews or overviews, commentaries or opinion papers, editorials/letters/comments, newspapers, trade journals, literature reviews, and guidelines were excluded. Studies with the absence of essential data were also excluded. VR and DC independently conducted the literature review. SS and GM independently evaluated the results obtained from VR and DC. After the completion of the literature review, researchers compiled and compared the results for any conflicts. Conflicts that arose were resolved through mutual consultation. Through the initial literature review, 22 articles were identified. Upon excluding duplicate studies and reading through the titles, abstracts, and methods, it was narrowed down to 6. Finally, 4 studies were selected for the analysis after full-text reading [Figure 2]. Data extraction was done by two researchers AK and AG independently from the selected studies.

Aggarwal *et al*. have reported performing RCE in SCA patients with multiple alloantibodies planned for surgery (arthroplasty). RCE procedure successfully reduced the HBS to the desired level and prevented postoperative complications. Here as the patient had multiple alloantibodies, corresponding antigen-negative red cell units were issued for the procedure.[20] Gupta *et al*. detailed emergency RCE as a life-saving modality in managing a case of SCA with acute chest syndrome and sepsis in their manuscript.[21] An original article by Daniel *et al*. showcased automated RCEs as a safe and efficient therapeutic procedure for acute management of SCA before surgery to avoid complications. Here 18 patients with SCD posted for surgery (hemiarthroplasty) were managed well with the single sitting of RCE and also

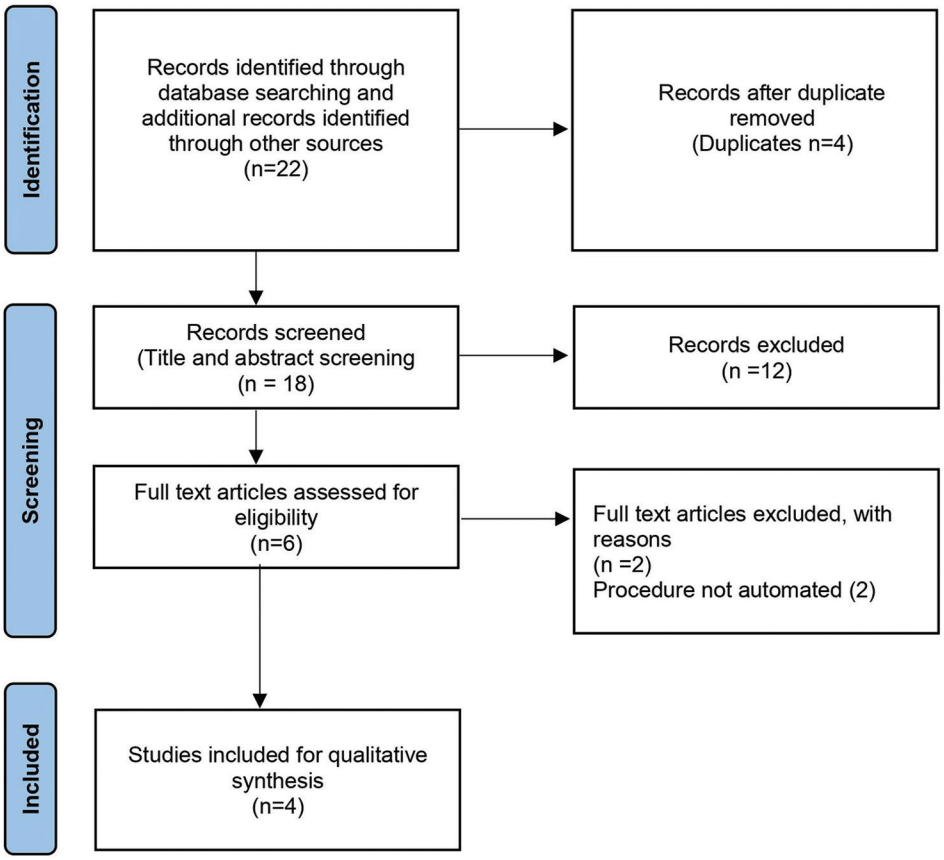

Figure 2: PRISMA chart showing the summary of data extraction history. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

reported RCEs as an underutilized therapy in developing countries.[22] Chowdhry *et al*. have reported RCEs as a simple and safe treatment modality for managing acute complications of SCA. They have mentioned that the target FCR was achieved in one or two sittings of RCE for all five patients and also commented on this as an underutilized therapeutic procedure.[23] Table 2 describes the various characteristics of the SCA cases in India managed by automated RCEs. A total of 25 patients underwent RCE as a therapeutic procedure with a preprocedure HBS ranging from 44.4% to 85%. The most common indication for automated RCEs in SCA in India through the review was found to be SCA patients posted for surgery (hemiarthroplasty). The procedure has shown good outcome in all the patients with a postprocedure HBS ranging from 9% to 29%. In contrast to this, Sahoo *et al*. reported on the four cases of SCA with vaso-occlusive crisis managed well with simple RCE. They also concluded manual RCEs as an affordable and effective measure to reduce the pain of severe vaso-occlusive crisis.[24]

Conclusion

Automated RCEs are promising as an acute treatment for indicated sickle cell complications. In the Indian scenario, this therapy is underutilized mostly due to the limited-resource setting, nonaffordability, and probable lack of awareness of its availability. Further studies may be conducted in India to explore the evidence of the efficacy of RCEs in the acute management of SCA crisis.

Consent

The patient consent for the publication and dissemination of data has been obtained.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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